Matrix Metalloproteinase-9 and its Inhibitor in Idiopathic Pulmonary Hemosiderosis

Sir,

Idiopathic pulmonary hemosiderosis (IPH) is characterized by recurrent episodes of diffuse alveolar hemorrhage and accumulation of hemosiderin in the lung. Examination of broncho-alveolar lavage (BAL) fluid (BALF) can disclose hemosiderin-laden alveolar macrophages, and the lung biopsy shows numerous siderophages in the alveoli and even pulmonary fibrosis at late stage. Matrix metalloproteinases (MMP) and its inhibitors (tissue matrix metalloproteinases inhibitor, TIMP) can degrade damaged matrix and maintain normal tissue homeostasis under normal circumstance. However, they may be produced in excess and contribute to tissue damage and activation of inappropriate repair mechanisms under pathologic conditions.

In the present study, we estimate the injury and matrix remodeling in children with IPH by investigating MMP-9 and TIMP-1 in BAL cells. Three children with IPH were enrolled (Table 1). BAL with saline was conducted in the right middle lobar during bronchoscopy. BAL cells were stained with Prussia.

Table 1. Characteristics of 3 Patients

	Case 1	Case 2	Case 3
Gender	Boy	Girl	Girl
Age (Year)	6.5	7.5	9.0
Duration (Year)	3	2	5
Hemoglobin (g/L)	106	87	91
WBC (109/L)	5.6	7.6	4.9
Platelet (109/L)	230	334	214
CRP (mg/dl)	<1	7	12
ESR (mm/h)	15	8	13
ANA	NA	Negative	Negative
PPD	Negative	Negative	Negative
ALT (U/L)	22	13	26
Blood Cre (μmol/L)		52.4	23.5 36.1
Chest imageology	Diffuse parenchymal infiltration in right lower field (X-ray)	Diffuse parenchymal infiltration in both sides (X-ray). Ground glass pattern and consolidated high density areas (CT)	Diffuse parenchymal infiltration in both sides (X-ray)

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibody; PPD, purified protein derivative of tuberculin; ALT, alanine aminotransferase; Cre, creatinine

MMP-9 and TIMP-1 were detected by monoclonal anti-human MMP-9 and TIMP-1 antibodies.

BALF of these patients were primrose yellow and numerous cells were noted. Except for red blood cells, 90-95% of BAL cells were macrophage, which was similar to that in normal children.[1] Consistent with previous studies,[2,3] all macrophages and lymphocytes in BALF of the 3 patients were positive for Prussian blue stain (Fig 1a), which suggested haemosiderin loading and supported the diagnosis of IPH.

Although IPH may be associated with an immunological or toxic mechanism causing defect in the basement membrane of the pulmonary capillary, the

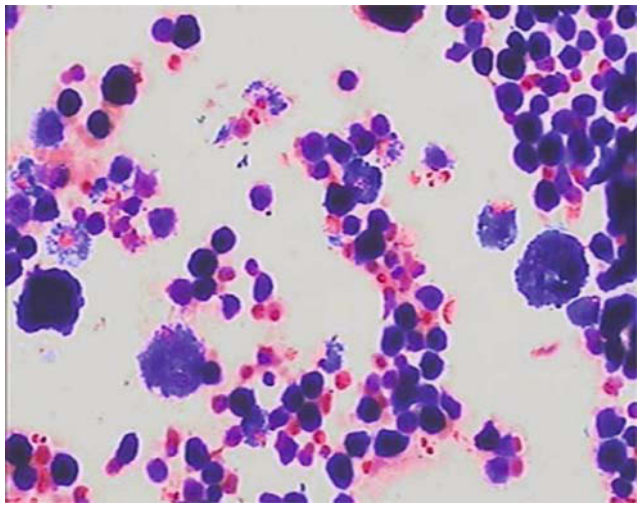

Fig. 1a

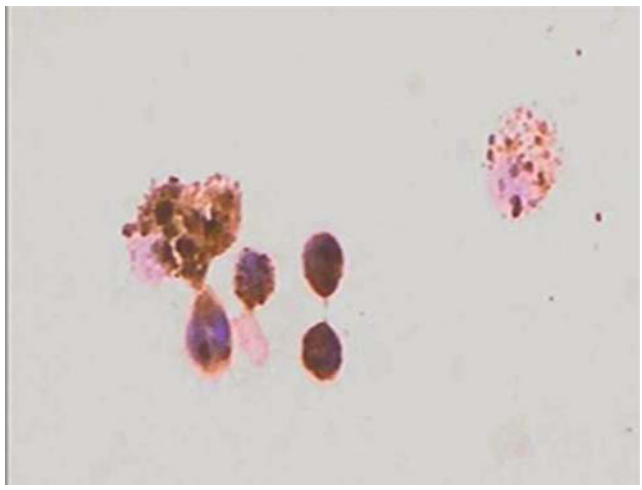

Fig. 1b

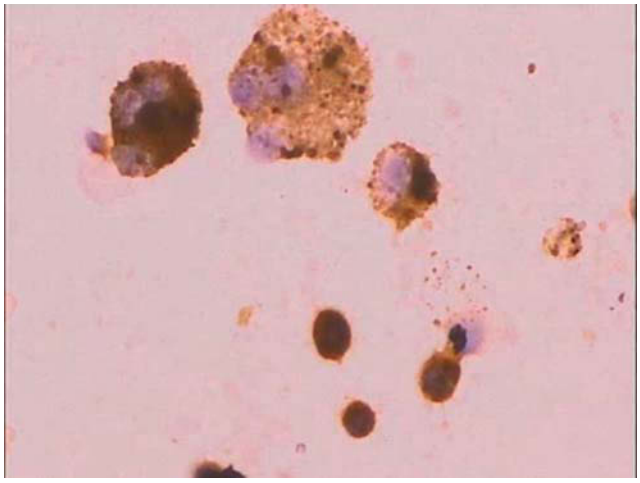

Fig. 1c

Fig 1. Immunocytochemistry of BAL cells in IPH patients. (a) Staining with Prussia showed that all macrophages were positive reaction (original magnification × 200). (b) All macrophages and lymphocytes showed a positive reaction for anti-MMP-9 antibody (original magnification × 400). (c) All macrophages and lymphocytes showed a positive reaction for anti-TIMP-1 antibody (original magnification × 400).

etiology is still unclear. To our knowledge, this is the first study on the role of MMP-9 and TIMP-1 in IPH. Our previous studies showed that MMP-9 and TIMP-1 were lowly expressed in normal lungs.[1] Here, we noted that nearly all macrophages and lymphocytes in BALF were strongly positive for MMP-9 and TIMP-1 (Fig 1b-c). The increased MMP-9 and TIMP-1 levels in inflammatory cells of BALF implied that they might play an important role in the pathogenesis of IPH. As MMP-9 plays an important role in the degradation of matrix, we speculated that elevated MMP-9 mediates the injury of the basement membrane in IPH. There are also growing evidence that MMP-9 may be crucial for the migration of airway inflammatory cells through matrix.[4] Hence, the increased generation of MMP-9 may be associated with the inflammatory acceleration, including the macrophages, neutrophils, and lymphocytes. TIMP-1 inhibits the degeneration of collagen and elastin mediated by MMP-9. Hence, increased TIMP-1 levels might be associated with progressive pulmonary fibrosis and lead to irreversible pulmonary dysfunction through causing inappropriate remodeling.

Studies showed that neutrophil and eosinophil are important source of MMP-9 and TIMP-1 in respiratory disease subjects.[5] According to our data, MMP-9 and TIMP-1 could be expressed in inflammatory cells from BALF, and the expression in macrophages and lymphocytes is very significant, which is consistent with our previous study.[1] This observation implies that the activation of airway inflammatory cells may be associated with the synthesis of MMP-9 and TIMP-1 and play a role in matrix turnover and airway remodeling.

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